M.R. HUTCHINS & CO

Chartered Patent Attorneys
European Patent Attorneys
European Trade Mark Attorneys
Registered Trade Mark Agents

23 Mount Sion
Tunbridge Wells
Kent TN1 1TZ
United Kingdom

Tel: 01892 539659
fax: 01892 528720
e-mail: mail@mrhutchins.com

The European Patent Office
Directorate General 2
Erhardstraße 27
D-80298 München 2
GERMANY

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23 July 2006

VIA FACSIMILE – ORIGINAL BY POST

Dear Sirs,

Re: European Patent Application No. 04806258.2
Derived from International Application No. PCT/GB2004/005464
International Publication No. WO 2005/061463
Applicants: (1) Astex Therapeutics Limited (2) Cancer Research Technology Limited & (3) The Institute of Cancer Research: Royal Cancer Hospital
Representative's Reference: AST20(EP)/MRH

We file herewith the following items in order to bring the above International application into the European Regional Phase.

1. A form 1200

2. Replacement pages 201 to 216 containing an amended set of claims which should form the basis for the further examination of this application.

3. A form 1037 for acknowledging safe receipt of this letter and the enclosures.

For the avoidance of doubt, we note that all amendments made at this stage are without prejudice to the later reinstatement of any deleted subject matter or the filing of a divisional application thereto.

The enclosed form 1200 contains a request for the fees due on this application to be debited from our deposit account by means of the automatic debiting procedure. However, if any further authorisation is needed, we request that this letter be taken as the necessary authorization to debit the deposit account of M.R. Hutchins & Co. (Deposit account no. 28050421) in respect of any outstanding fees.

A form 1037 is enclosed.

Yours faithfully

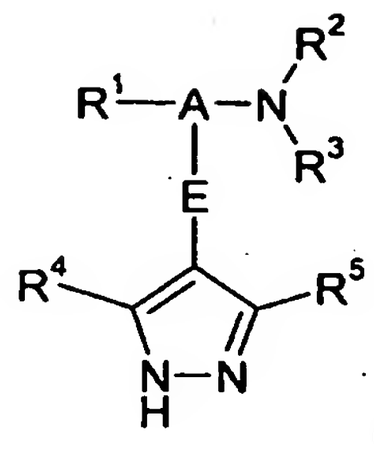
M. R. HUTCHINS & CO

Dr Michael R. Hutchins

Authorized Representative

CLAIMS

1. A compound of the formula (I):



(I)

or a salt, solvate, tautomer or N-oxide thereof;

wherein A is a saturated hydrocarbon linker group containing from 1 to 7 carbon atoms, the linker group having a maximum chain length of 5 atoms extending between R^1 and NR^2R^3 and a maximum chain length of 4 atoms extending between E and NR^2R^3, wherein one of the carbon atoms in the linker group may optionally be replaced by an oxygen or nitrogen atom; and wherein the carbon atoms of the linker group A may optionally bear one or more substituents selected from oxo, fluorine and hydroxy, provided that the hydroxy group when present is not located at a carbon atom α with respect to the NR^2R^3 group and provided that the oxo group when present is located at a carbon atom α with respect to the NR^2R^3 group;

E is a monocyclic or bicyclic carbocyclic or heterocyclic group;

R^1 is an aryl or heteroaryl group;

R^2 and R^3 are independently selected from hydrogen, C_{1-4} hydrocarbyl and C_{1-4} acyl wherein the hydrocarbyl and acyl moieties are optionally substituted by one or more substituents selected from fluorine, hydroxy, amino, methylamino, dimethylamino and methoxy;

or R^2 and R^3 together with the nitrogen atom to which they are attached form a cyclic group selected from an imidazole group and a saturated monocyclic

heterocyclic group having 4-7 ring members and optionally containing a second heteroatom ring member selected from O and N;

or one of R^2 and R^3 together with the nitrogen atom to which they are attached and one or more atoms from the linker group A form a saturated monocyclic heterocyclic group having 4-7 ring members and optionally containing a second heteroatom ring member selected from O and N;

or NR^2R^3 and the carbon atom of linker group A to which it is attached together form a cyano group;

R^4 is selected from hydrogen, halogen, C_{1-5} saturated hydrocarbyl, C_{1-5} saturated hydrocarbyloxy, cyano, and CF_3; and

R^5 is selected from hydrogen, halogen, C_{1-5} saturated hydrocarbyl, C_{1-5} saturated hydrocarbyloxy, cyano, $CONH_2$, $CONHR^9$, CF_3, NH_2, $NHCOR^9$ or $NHCONHR^9$;

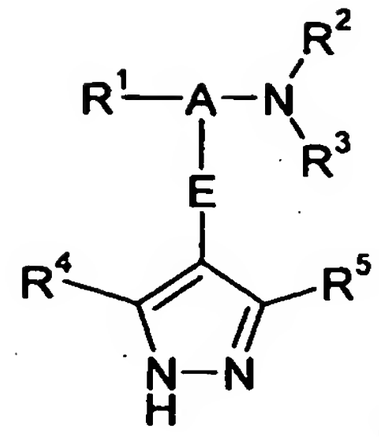
R^9 is a group R^{9a} or $(CH_2)R^{9a}$, wherein R^{9a} is a monocyclic or bicyclic group which may be carbocyclic or heterocyclic;

the carbocyclic group or heterocyclic group R^{9a} being optionally substituted by one or more substituents selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino; a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^c, SO_2NR^c or NR^cSO_2; and R^b is selected from hydrogen, heterocyclic groups having from 3 to 12 ring members, and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

R^c is selected from hydrogen and C_{1-4} hydrocarbyl; and

X^1 is O, S or NR^c and X^2 is =O, =S or =NR^c.

2. A compound according to claim 1 of the formula (Ia):



(Ia)

or a salt, solvate, tautomer or N-oxide thereof;

wherein A is a saturated hydrocarbon linker group containing from 1 to 7 carbon atoms, the linker group having a maximum chain length of 5 atoms extending between R^1 and NR^2R^3 and a maximum chain length of 4 atoms extending between E and NR^2R^3, wherein one of the carbon atoms in the linker group may optionally be replaced by an oxygen or nitrogen atom; and wherein the carbon atoms of the linker group A may optionally bear one or more substituents selected from oxo, fluorine and hydroxy, provided that the hydroxy group when present is not located at a carbon atom α with respect to the NR^2R^3 group and provided that the oxo group when present is located at a carbon atom α with respect to the NR^2R^3 group;

E is a monocyclic or bicyclic carbocyclic or heterocyclic group;

R^1 is an aryl or heteroaryl group;

R^2 and R^3 are independently selected from hydrogen, C_{1-4} hydrocarbyl and C_{1-4} acyl;

or R^2 and R^3 together with the nitrogen atom to which they are attached form a saturated monocyclic heterocyclic group having 4-7 ring members and optionally containing a second heteroatom ring member selected from O and N;

or one of R^2 and R^3 together with the nitrogen atom to which they are attached and one or more atoms from the linker group A form a saturated monocyclic heterocyclic group having 4-7 ring members and optionally containing a second heteroatom ring member selected from O and N;

or NR^2R^3 and the carbon atom of linker group A to which it is attached together form a cyano group;

R^4 is selected from hydrogen, halogen, C_{1-5} saturated hydrocarbyl, cyano and CF_3; and

R^5 is selected from hydrogen, halogen, C_{1-5} saturated hydrocarbyl, cyano, $CONH_2$, $CONHR^9$, CF_3, NH_2, $NHCOR^9$ or $NHCONHR^9$;

R^9 is phenyl or benzyl each optionally substituted by one or more substituents selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino; a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^c, SO_2NR^c or NR^cSO_2; and R^b is selected from hydrogen, heterocyclic groups having from 3 to 12 ring members, and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

R^c is selected from hydrogen and C_{1-4} hydrocarbyl; and

X^1 is O, S or NR^c and X^2 is =O, =S or =NR^c.

3. A compound according to claim 1 or claim 2 wherein A is a saturated hydrocarbon linker group containing from 1 to 7 carbon atoms, the linker group having a maximum chain length of 5 atoms extending between R^1 and NR^2R^3 and a maximum chain length of 4 atoms extending between E and NR^2R^3, wherein one of the carbon atoms in the linker group may optionally be replaced by an oxygen or nitrogen atom; and wherein the carbon atoms of the linker group A may optionally bear one or more substituents selected from fluorine and hydroxy, provided that the hydroxy group when present is not located at a carbon atom α with respect to the NR^2R^3 group; and

R^5 is selected from selected from hydrogen, halogen, C_{1-5} saturated hydrocarbyl, cyano, $CONH_2$, CF_3, NH_2, $NHCOR^9$ and $NHCONHR^9$.

4. A compound according to any one of claims 1 to 3 wherein:

(i) the linker group A has a maximum chain length of 3 atoms (more preferably 1 or 2 atoms, and most preferably 2 atoms) extending between R^1 and NR^2R^3; and/or

(ii) the linker group A has a maximum chain length of 3 atoms extending between E and NR^2R^3; and/or

(iii) the linker group A has a chain length of 2 or 3 atoms extending between R^1 and NR^2R^3 and a chain length of 2 or 3 atoms extending between E and NR^2R^3; and/or

(iv) the linker group atom linked directly to the group E is a carbon atom and the linker group A has an all-carbon skeleton.

5. A compound according to any one of claims 1 to 3 wherein the portion R^1-A-NR^2R^3 of the compound is represented by the formula R^1-$(G)_k$-$(CH_2)_m$-W-O_b-$(CH_2)_n$-$(CR^6R^7)_p$-NR^2R^3 wherein G is NH, NMe or O; W is attached to the group E and is selected from $(CH_2)_j$-CR^{20}, $(CH_2)_j$-N and $(NH)_j$-CH; b is 0 or 1, j is 0 or 1, k is 0 or 1, m is 0 or 1, n is 0, 1, 2, or 3 and p is 0 or 1; the sum of b and k is 0 or 1; the sum of j, k, m, n and p does not exceed 4; R^6 and R^7 are the same or different and are selected from methyl and ethyl, or CR^6R^7 forms a cyclopropyl group; and R^{20} is selected from hydrogen, methyl, hydroxy and fluorine.

6. A compound according to any one of claims 1 to 3 wherein the moiety R^1-A-NR^2R^3 is represented by the formula R^1-$(G)_k$-$(CH_2)_m$-X-$(CH_2)_n$-$(CR^6R^7)_p$-NR^2R^3 wherein G is NH, NMe or O; X is attached to the group E and is selected from $(CH_2)_j$-CH, $(CH_2)_j$-N and $(NH)_j$-CH; j is 0 or 1, k is 0 or 1, m is 0 or 1, n is 0, 1, 2, or 3 and p is 0 or 1, and the sum of j, k, m, n and p does not exceed 4; and R^6 and R^7 are the same or different and are selected from methyl and ethyl, or CR^6R^7 forms a cyclopropyl group.

7. A compound according to claim 6 wherein (i) k is 0, m is 0 or 1, n is 0, 1, 2 or 3 and p is 0; or (ii) k is 0, m is 0 or 1, n is 0, 1 or 2 and p is 1.

8. A compound according to claim 6 wherein (i) X is $(CH_2)_j$-CH, k is 1, m is 0, n is 0, 1,2 or 3 and p is 0; or (ii) X is $(CH_2)_j$-CH, k is 1, m is 0, n is 0, 1 or 2 and p is 1.

9. A compound according to claim 6 or claim 8 wherein (i) j is 0; or (ii) j is 1; or (iii) CR^6R^7 is $C(CH_3)_2$.

10. A compound according to claim 6 wherein the portion R^1-A-NR^2R^3 of the compound is represented by the formula R^1-X-$(CH_2)_n$-NR^2R^3 where X is attached to the group E and is a group CH, and n is 2.

11. A compound according to claim 1 or claim 2 wherein R^1-A(E)-NR^2R^3 is (i) a group selected from the groups A1 to A11 set out in Table 1 herein; or (ii) is selected from groups A1, A2, A3 and A10 in Table 1; or (iii) is the group A10 in Table 1.

12. A compound according to any one of the preceding claims wherein:

(a) E is an aryl or heteroaryl group such as optionally substituted phenyl, thiophene, furan, pyrimidine and pyridine groups; or

(b) E is a phenyl group; or

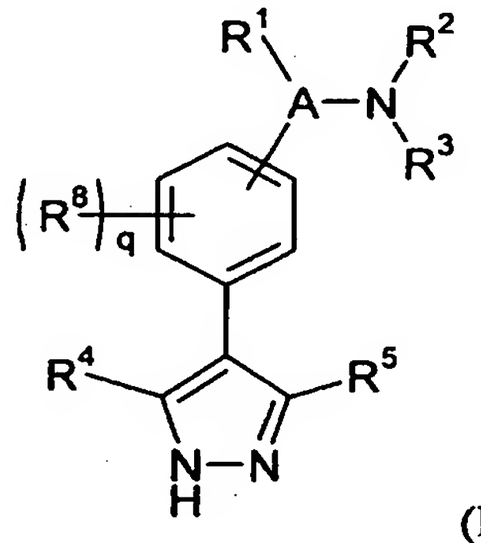
(c) E is a non-aromatic monocyclic group selected from cycloalkanes such as cyclohexane and cyclopentane, and nitrogen-containing rings such as piperazine and piperazone; or

(d) E is a monocyclic group.

13. A compound according to any one of the preceding claims wherein the group A and the pyrazole group are attached to the group E in a *meta* or *para* relative orientation; i.e. A and the pyrazole group are not attached to adjacent ring members of the group E, for example wherein E is selected from 1,4-phenylene, 1,3-phenylene, 2,5-pyridylene and 2,4-pyridylene, 1,4-piperazinyl, and 1,4-piperazonyl.

14. A compound according to any one of the preceding claims wherein E is (i) unsubstituted or (ii) has up to 4 substituents (e.g. 0-3 substituents, more preferably 0-2 substituents, for example 0 or 1 substituent) R^8 selected from hydroxy, oxo (when E is non-aromatic), chlorine, bromine, trifluoromethyl, cyano, C_{1-4} hydrocarbyloxy and C_{1-4} hydrocarbyl optionally substituted by C_{1-2} alkoxy or hydroxy.

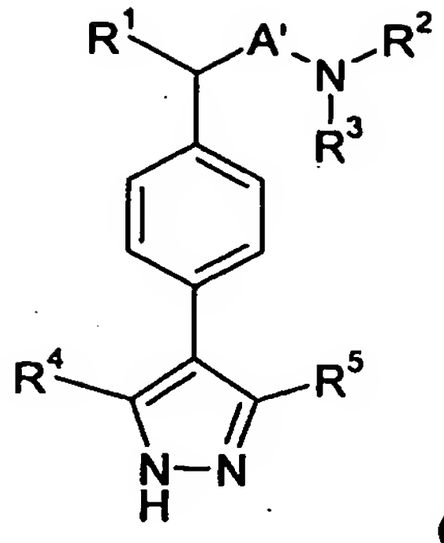
15. A compound according to claim 12 having the formula (II):



(II)

wherein the group A is attached to the *meta* or *para* position of the benzene ring and q is 0-4 (for example wherein q is 0, 1 or 2, preferably 0 or 1 and most preferably 0); R^8 is hydroxy; halogen (e.g. chlorine and bromine); trifluoromethyl; cyano; C_{1-4} hydrocarbyloxy optionally substituted by C_{1-2} alkoxy or hydroxy; and C_{1-4} hydrocarbyl optionally substituted by C_{1-2} alkoxy or hydroxy.

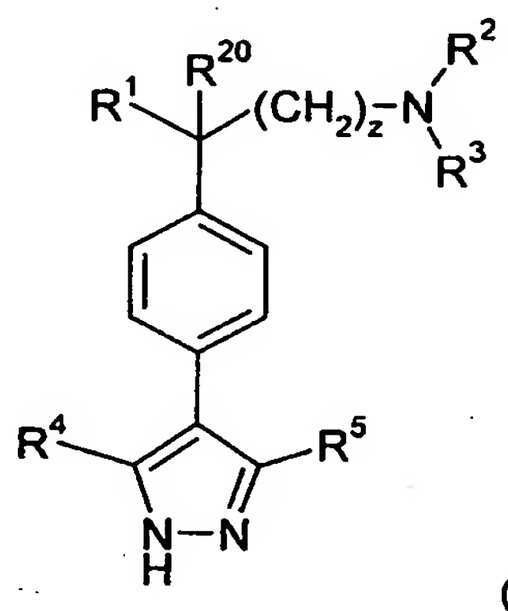
16. A compound according to claim 13 having the formula (III):



(III)

where A' is the residue of the group A and R^1 to R^5 are as defined in any one of the preceding claims.

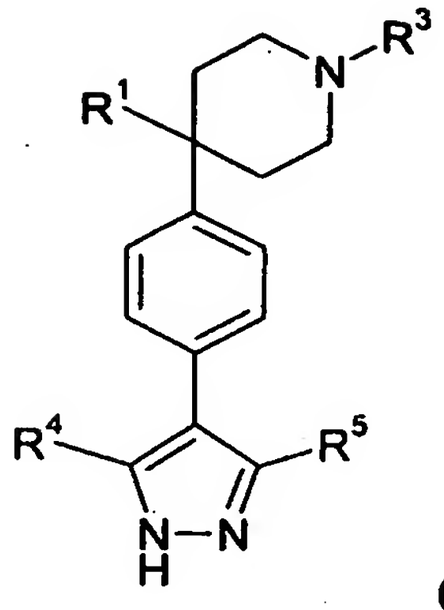
17. A compound according to claim 15 having the formula (IV):



(IV)

wherein z is 0, 1 or 2, R^{20} is selected from hydrogen, methyl, hydroxy and fluorine, provided that when z is 0, R^{20} is other than hydroxy.

18. A compound according to claim15 having the formula (V):



(V)

wherein R^3 is optionally selected from hydrogen and C_{1-4} hydrocarbyl, for example C_{1-4} alkyl such as methyl, ethyl and isopropyl, and more preferably R^3 is hydrogen.

19. A compound according to any one of the preceding claims wherein R^1 is selected from phenyl, naphthyl, thienyl, furan, pyrimidine and pyridine, and preferably wherein R^1 is phenyl.

20. A compound according to any one of the preceding claims wherein R^1 is unsubstituted or bears one or more substituents selected from hydroxy; C_{1-4} acyloxy; fluorine; chlorine; bromine; trifluoromethyl; cyano; $CONH_2$; nitro; C_{1-4} hydrocarbyloxy and C_{1-4} hydrocarbyl each optionally substituted by C_{1-2} alkoxy, carboxy or hydroxy; C_{1-4} acylamino; benzoylamino; pyrrolidinocarbonyl; piperidinocarbonyl; morpholinocarbonyl; piperazinocarbonyl; five and six membered heteroaryl and heteroaryloxy groups containing one or two heteroatoms selected from N, O and S; phenyl; phenyl-C_{1-4} alkyl; phenyl-C_{1-4} alkoxy; heteroaryl-C_{1-4} alkyl; heteroaryl-C_{1-4} alkoxy and phenoxy, wherein the heteroaryl, heteroaryloxy, phenyl, phenyl-C_{1-4} alkyl, phenyl-C_{1-4} alkoxy, heteroaryl-C_{1-4} alkyl, heteroaryl-C_{1-4} alkoxy and phenoxy groups are each optionally substituted with 1, 2 or 3 substituents selected from C_{1-2} acyloxy, fluorine, chlorine, bromine, trifluoromethyl, cyano, $CONH_2$, C_{1-2} hydrocarbyloxy and C_{1-2} hydrocarbyl each optionally substituted by methoxy or hydroxy.

21. A compound according to claim 20 wherein:

(a) R^1 is unsubstituted or is substituted by up to 5 substituents (e.g. 0, 1, 2, 3 or 4 substituents, preferably 0, 1, 2 or 3, and more preferably 0, 1or 2 substituents) selected from hydroxy; C_{1-4} acyloxy; fluorine; chlorine; bromine; trifluoromethyl; cyano; C_{1-4} hydrocarbyloxy and C_{1-4} hydrocarbyl optionally substituted by C_{1-2} alkoxy or hydroxy; and five membered heteroaryl groups containing one or two heteroatoms selected from N, O and S, the heteroaryl groups being optionally substituted by one or more C_{1-4} alkyl substituents; or

(b) R^1 is unsubstituted or is substituted by up to 5 substituents (e.g. 0, 1, 2, 3 or 4 substituents, preferably 0, 1, 2 or 3, and more preferably 0, 1or 2 substituents) selected from hydroxy, C_{1-4} acyloxy, fluorine, chlorine, bromine, trifluoromethyl, cyano, C_{1-4} hydrocarbyloxy and C_{1-4} hydrocarbyl optionally substituted by C_{1-2} alkoxy or hydroxy.

22. A compound according to claim 21 wherein the group R^1 has one or two substituents selected from fluorine, chlorine, trifluoromethyl, methyl and methoxy.

23. A compound according to claim 22 wherein R^1 is a mono-chlorophenyl or dichlorophenyl group.

24. A compound according to any one of the preceding claims wherein (a) R^4 is selected from hydrogen and methyl; and/or (b) R^5 is selected from hydrogen, fluorine, chlorine, bromine, methyl, ethyl, hydroxyethyl, methoxymethyl, cyano, CF_3, NH_2, $NHCOR^{9b}$ and $NHCONHR^{9b}$ where R^{9b} is phenyl or benzyl optionally substituted by hydroxy, C_{1-4} acyloxy, fluorine, chlorine, bromine, trifluoromethyl, cyano, C_{1-4} hydrocarbyloxy and C_{1-4} hydrocarbyl optionally substituted by C_{1-2} alkoxy or hydroxy.

25. A compound according to any one of the preceding claims wherein:

(a) R^2 and R^3 are independently selected from hydrogen, C_{1-4} hydrocarbyl and C_{1-4} acyl; or

(b) R^2 and R^3 are independently selected from hydrogen and methyl; or

(c) R^2 and R^3 are both hydrogen.

26. A compound according to any one of the preceding claims having a molecular weight no greater than 1000, more usually less than 750, for example less than 700, or less than 650, or less than 600, or less than 550, or less than 525, for example 500 or less.

27. A compound of the formula (I) which is:

2-phenyl-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethylamine;

3-phenyl-2-[3-(1H-pyrazol-4-yl)-phenyl]-propionitrile;

2-[4-(3,5-dimethyl-1H-pyrazol-4-yl)-phenyl]-2-phenyl-ethylamine;

2-(4-chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethylamine;

2-[3-(3,5-dimethyl-1H-pyrazol-4-yl)-phenyl]-1-phenyl-ethylamine;

3-phenyl-2-[3-(1H-pyrazol-4-yl)-phenyl]-propylamine;

3-phenyl-2-[4-(1H-pyrazol-4-yl)-phenyl]-propylamine;

{3-(4-chloro-phenyl)-3-[4-(1H-pyrazol-4-yl)-phenyl]-propyl}-methyl-amine;

{3-(3,4-difluoro-phenyl)-3-[4-(1H-pyrazol-4-yl)-phenyl]-propyl}-methyl-amine;

{3-(3-chloro-phenyl)-3-[4-(1H-pyrazol-4-yl)-phenyl]-propyl}-methyl-amine;

3-(4-chloro-phenyl)-3-[4-(1H-pyrazol-4-yl)-phenyl]-propionamide;

3-(4-chloro-phenyl)-3-[4-(1H-pyrazol-4-yl)-phenyl]-propylamine;

3-(3,4-dichloro-phenyl)-3-[4-(1H-pyrazol-4-yl)-phenyl]-propylamine;

4-(4-chloro-phenyl)-4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine;

4-(4-methoxy-phenyl)-4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine;

4-(4-chloro-phenyl)-1-methyl-4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine;

4-phenyl-4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine;

4-[4-(3,5-dimethyl-1H-pyrazol-4-yl)-phenyl]-4-phenyl-piperidine;

dimethyl-{3-[4-(1H-pyrazol-4-yl)-phenyl]-3-pyridin-2-yl-propyl}-amine;

{2-(4-chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-dimethyl-amine;

{2-(4-chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-methyl-amine;
{2-(4-chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-methyl-amine (R);
{2-(4-chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-methyl-amine (S);
4-{2-(4-chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-morpholine;
4-{4-[1-(4-chloro-phenyl)-2-pyrrolidin-1-yl-ethyl]-phenyl}-1H-pyrazole;
{2-(4-chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-isopropyl-amine;
dimethyl-{2-phenyl-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-amine;
{2,2-bis-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-dimethyl-amine;
{2,2-bis-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-methyl-amine;
2-(4-chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethylamine (R);
2-(4-chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethylamine (S);
2-(4-chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-acetamide;
1-{2-(4-chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-piperazine;
1-{2-(4-chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-piperidine;
4-{4-[2-azetidin-1-yl-1-(4-chloro-phenyl)-ethyl]-phenyl}-1H-pyrazole;
1-phenyl-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethylamine;
2-(4-chloro-phenyl)-N-methyl-2-[4-(1H-pyrazol-4-yl)-phenyl]-acetamide;
N-methyl-2,2-bis-[4-(1H-pyrazol-4-yl)-phenyl]-acetamide;
{2-(4-chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-methyl-amine;
{2-(4-chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-ethyl-amine;
4-{4-[1-(4-chloro-phenyl)-2-imidazol-1-yl-ethyl]-phenyl}-1H-pyrazole;
methyl-{2-(4-phenoxy-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-amine;
{2-(4-methoxy-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-methyl-amine;
methyl-{2-[4-(pyrazin-2-yloxy)-phenyl]-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-amine;
methyl-{2-phenoxy-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-amine;
2-{(4-chloro-phenyl)-[4-(1H-pyrazol-4-yl)-phenyl]-methoxy}-ethylamine;
4-{4-[1-(4-chloro-phenyl)-3-pyrrolidin-1-yl-propyl]-phenyl}-1H-pyrazole;
4-{4-[3-azetidin-1-yl-1-(4-chloro-phenyl)-propyl]-phenyl}-1H-pyrazole;
methyl-{3-naphthalen-2-yl-3-[4-(1H-pyrazol-4-yl)-phenyl]-propyl}-amine;

dimethyl-(4-{3-methylamino-1-[4-(1H-pyrazol-4-yl)-phenyl]-propyl}-phenyl)-amine;

{3-(4-fluoro-phenyl)-3-[4-(1H-pyrazol-4-yl)-phenyl]-propyl}-methyl-amine;

4-{4-[4-(4-chloro-phenyl)-piperidin-4-yl]-phenyl}-1H-pyrazole-3-carbonitrile;

3-(4-phenoxy-phenyl)-3-[4-(1H-pyrazol-4-yl)-phenyl]-propylamine;

1-{(4-chloro-phenyl)-[4-(1H-pyrazol-4-yl)-phenyl]-methyl}-piperazine;

1-methyl-4-{phenyl-[4-(1H-pyrazol-4-yl)-phenyl]-methyl}-[1,4]diazepane;

{3-(3-chloro-phenoxy)-3-[4-(1H-pyrazol-4-yl)-phenyl]-propyl}-methyl-amine;

methyl-{2-phenyl-2-[6-(1H-pyrazol-4-yl)-pyridin-3-yl]-ethyl}-amine;

4-{4-[1-(4-chloro-phenyl)-3-imidazol-1-yl-propyl]-phenyl}-1H-pyrazole;

4-[4-(3-imidazol-1-yl-1-phenoxy-propyl)-phenyl]-1H-pyrazole;

4-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-phenol;

1-{(4-chloro-phenyl)-[4-(1H-pyrazol-4-yl)-phenyl]-methyl}-piperazine;

{2-(4-fluoro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-methyl-amine;

{2-(3-chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-methyl-amine;

4-[4-(2-methoxy-ethoxy)-phenyl]-4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine;

4-[4-(3-methoxy-propoxy)-phenyl]-4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine;

3-(3,4-dichloro-phenyl)-3-[4-(1H-pyrazol-4-yl)-phenyl]-propionamide;

2-(4-{2-methylamino-1-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-phenoxy)-isonicotinamide;

{2-(3-chloro-phenoxy)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-methyl-amine;

3-{2-(4-chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethylamino}-propan-1-ol;

2-{2-(4-chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethylamino}-ethanol;

3-{2-(4-chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethylamino}-propan-1-ol;

2-{2-(4-chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethylamino}-ethanol;

{2-(4-chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-cyclopropylmethyl-amine;

methyl-[2-[4-(1H-pyrazol-4-yl)-phenyl]-2-(4-pyridin-3-yl-phenyl)-ethyl]-amine;

4-{3-methylamino-1-[4-(1H-pyrazol-4-yl)-phenyl]-propyl}-phenol;

3-(4-methoxy-phenyl)-3-[4-(1H-pyrazol-4-yl)-phenyl]-propylamine;

4-(4-chloro-phenyl)-4-[4-(3-methyl-1H-pyrazol-4-yl)-phenyl]-piperidine;
2-(4-chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-morpholine;
(4-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-phenoxy)-acetic acid;
(4-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-phenoxy)-acetic acid, methyl ester;
4-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-benzonitrile;
{2-(4-chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-propyl}-methyl-amine;
1-(4-chloro-phenyl)-2-methylamino-1-[4-(1H-pyrazol-4-yl)-phenyl]-ethanol;
2-amino-1-(4-chloro-phenyl)-1-[4-(1H-pyrazol-4-yl)-phenyl]-ethanol;
4-(3,4-dichloro-phenyl)-4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine;
4-(3-chloro-4-methoxy-phenyl)-4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine;
4-(4-chloro-3-fluoro-phenyl)-4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine;
4-{4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidin-4-yl}-benzoic acid;
4-[4-(1H-pyrazol-4-yl)-phenyl]-1,2,3,4,5,6-hexahydro-[4,4']bipyridinyl;
3-(3-chloro-phenyl)-3-[4-(1H-pyrazol-4-yl)-phenyl]-propylamine;
2-methylamino-1-(4-nitro-phenyl)-1-[4-(1H-pyrazol-4-yl)-phenyl]-ethanol;
2-(3-chloro-4-methoxy-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethylamine;
2-(4-chloro-phenyl)-2-fluoro-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethylamine;
3-(3,4-dichloro-phenyl)-3-[6-(1H-pyrazol-4-yl)-pyridin-3-yl]-propylamine;
2-(4-chloro-3-fluoro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethylamine;
4-(2-chloro-3-fluoro-phenyl)-4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine;
1-{(3,4-dichloro-phenyl)-[4-(1H-pyrazol-4-yl)-phenyl]-methyl}-piperazine;
2-(3,4-dichloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethylamine;
{2-(3-chloro-4-methoxy-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-methyl-amine;
4-{4-[2-azetidin-1-yl-1-(4-chloro-phenoxy)-ethyl]-phenyl}-1H-pyrazole;
3-(3-chloro-4-methoxy-phenyl)-3-[4-(1H-pyrazol-4-yl)-phenyl]-propylamine;
{3-(3-chloro-4-methoxy-phenyl)-3-[4-(1H-pyrazol-4-yl)-phenyl]-propyl}-methyl-amine;
1-{(3,4-dichloro-phenyl)-[4-(1H-pyrazol-4-yl)-phenyl]-methyl}-piperazine; or

C-(4-chloro-phenyl)-C-[4-(1H-pyrazol-4-yl)-phenyl]-methylamine;
and salts, solvates, tautomers and N-oxides thereof.

28. A compound according to any one of the preceding claims in the form of a salt, solvate (such as a hydrate), ester or N-oxide.

29. A compound as defined in any one of claims 1 to 28 for use in medicine; for example (a) for use in the prophylaxis or treatment of a disease state or condition mediated by protein kinase B; or (b) for use in the prophylaxis or treatment of a disease state or condition mediated by protein kinase A.

30. The use of a compound as defined in any one of claims 1 to 28 for:

(a) the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by protein kinase B; or

(b) the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by protein kinase A; or

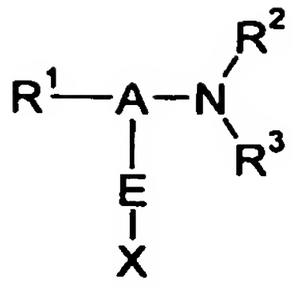
(c) the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition arising from abnormal cell growth;

(d) the manufacture of a medicament for the prophylaxis or treatment of a disease in which there is a disorder of proliferation, apoptosis or differentiation.

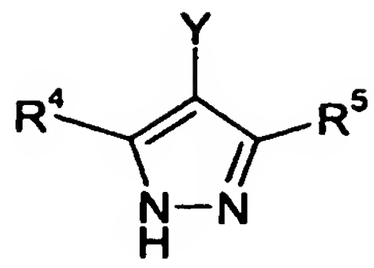
31. A pharmaceutical composition comprising a novel compound as defined in any one of claims 1 to 28 and a pharmaceutically acceptable carrier.

32. A process for the preparation of a compound of the formula (I) as defined in any one of claims 1 to 28, which process comprises:

(a) the reaction of a compound of the formula (X) with a compound of the formula (XI) or an N-protected derivative thereof:



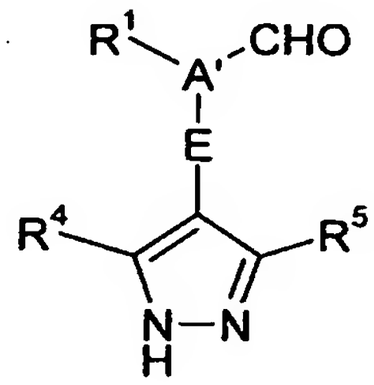
(X)



(XI)

wherein A, E, and R^1 to R^5 are as defined in any one of the preceding claims, one of the groups X and Y is selected from chlorine, bromine, iodine and trifluoromethanesulphonate, and the other one of the groups X and Y is a boronate residue, for example a boronate ester or boronic acid residue, in the presence of a palladium catalyst and a base;

(b) the reductive amination of a compound of the formula (XXXVI):



(XXXVI)

with HNR^2R^3 in the presence of a reducing agent; and optionally

(c) the conversion of one compound of the formula (I) into another compound of the formula (I).